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09/804,464	03/13/2001	Thomas M. Kundig	05184.00002	8772

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	

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10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/804,464	Applicant(s) KUNDIG ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,14,19-26,45 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,14,19-26,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/9/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-10, 14, 19-26 and 45-46 are pending.

2. In view of the amendment filed 1/9/03, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10, 14, 19-26 and 45-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method of desensitizing any individual to an allergen comprising the step of delivering allergen phospholipase A2 purified from bee venom against which the individual mounts an allergic response directly to the lymph node such as the axillary lymph node or inguinal lymph node of said individual whereby the individual is desensitized to the allergen using an ultrasound devise to monitor the location of an injection needle; (2) the said method wherein the allergen is delivered to an antigen presenting cell within said lymph node or an immune cell within said lymph node and (3) the said method further comprising the step of visualizing the lymph node using a radiological method for increasing antigen specific IgG2a and a decrease in antigen specific IgE, **does not** reasonably provide enablement for (1) a method of desensitizing an individual to *any* allergen comprising the step of delivering any allergen against which the individual mounts an allergic response directly to any lymph node of said individual whereby the individual is desensitized to the allergen, (2) the said method wherein the lymph node is an axillary lymph node or inguinal lymph node, (3) the said method wherein the allergen is allergen is deliver to an antigen presenting cell or an immune cell within the lymph node, (4) the said method further comprises the steps of using an ultrasound device to monitor location of an injection needle, (5) the said method further comprises the steps of visualizing the lymph node using a radiological method, (6) the said method wherein the allergen is *any* extract, or *any* "purified substance", *any* recombinant protein, *any* synthesized peptide, (7) the said method wherein the allergen is accompanied by an adjuvant such as *any* surface active agent, *any* surface active microparticle, *any* bacterial product, *any* cytokine, *any* hormone, any cellulose derivative, any protein, and any nucleic acid, (8) the said method wherein

the step of delivering is carried out at least twice, (9) the said method wherein 1 to 5 doses of from about 0.01 μg to about 10 μg, or from about 0.1 μg to about 50 μg of the allergen is administered, (10) the said method wherein the allergen is deliver in fewer than about 10 doses, or from 1 to about 5 doses and (11) the said method wherein the allergen is delivered into the lymph node with a syringe or a dual-chambered syringe for desensitize an individual to *any* allergic response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of desensitizing an individual to an allergen comprising the step of delivering allergen wherein the allergen is phospholipase A2 which is an allergic component of bee venom against which the individual mounts an allergic response, directly to the lymph node such as the axillary lymph node or inguinal lymph node of said individual whereby the individual is desensitized to said allergen. The specification further discloses that an ultrasound device is used to monitor the location of the injection needle, and/or visualizing the lymph node using a radiological method. The specification discloses bee sting challenge only produces a minimum local reaction in a patient who has been desensitized.

The specification does not teach how to desensitizing an individual using *any* allergen such as "purified substance", *any* "recombinant protein" and *any* "synthesized peptide", *any* "components" from bee venom, wasp venom, fire ant venom, pollen, mold, anesthetics, serum, drugs, animals, animal dander, cockroaches, dust mites, food allergen, poison ivy, poison oak, poison sumac, viruses, bacteria, protozoa, and latex because the specification does not define the term "substance", and "components". There is insufficient guidance as to the structure of *any* "purified substance", "recombinant protein", "synthesized peptide", "components" and "substance" mentioned above without the amino acid sequence or SEQ ID NO. In the absence of

guidance as to the structure and the lack of sufficient working example, it is unpredictable which undisclosed "purified substance", "recombinant protein", "synthesized peptide", "components" and "substance" of any allergen mentioned above are critical for the claimed method. Further, there is insufficient guidance as to the structure of *any* adjuvant such as *any* surface active agent, *any* surface active microparticle, *any* bacterial product, *any* cytokine, *any* hormone, *any* cellulose derivative, *any* protein without the specific amino acid sequence and any nucleic acid without the nucleotide sequence, much less about the function.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities.

Given the indefinite number of undisclosed "purified substance", *any* "recombinant protein", *any* "synthesized peptide", and "components" of any allergen and an indefinite number of undisclosed surface active agent, surface active microparticle, bacterial product, cytokine, hormone, cellulose derivative, protein, and nucleic acid that could be used as an adjuvant for the claimed method of desensitization, a person of skill in the art would not know which undisclosed "purified substance", "recombinant protein", "synthesized peptide", "components" of allergen is essential and which undisclosed surface active agent, surface active microparticle, bacterial product, cytokine, hormone, cellulose derivative, protein, and nucleic acid that could be used as an adjuvant. The experimentation left to those skilled in the art is unnecessarily, improperly, extensive and undue.

Even if the claimed method of desensitizing an individual is limited to allergen, the amended claim 1 fails to recite the step of how to deliver the allergen to any lymph node because the step of monitoring the location of an injection needle within the lymph node is critical for the claimed method.

Guidry *et al* teach lymph node injection of a substance such as Staphylococcus aureus significantly increase IgG2 response and the IgG2 response was slower and peak later than that for IgG1 (See page 2968, column 1, results, in particular). Guidry *et al* teach lymph node injection fails to elicit IgA response although IgA tended to be slightly higher than the IgM response. Given the indefinite number of undisclosed allergen, extract, substance, recombinant protein and synthesized peptide, it is unpredictable which undisclosed substance, recombinant protein, synthesized peptide mentioned above would be useful for desensitizing an individual any allergy. Other than the specific allergen mentioned above, the method of desensitizing an individual using any undisclosed allergen such as any extract, *any* purified substance, *any* recombinant protein and *any* synthesized peptide is not enabled; it follows that the dose of *any* undisclosed allergen mentioned above is not enabled. It also follows that the method of modulating an allergic response further comprising the step of using an ultrasound device, or radiological method is not enable.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 1/9/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the novel aspect of the invention is the intranodal injection of an allergen to desensitize an individual to the allergen. (2) In spite of the clear teachings of the specification and the prior art, the Office appears to doubt that intranodal injection of allergens would work as described. (3) The Gidry reference is directed to immunization of cows against S aureus infection and contains no teaching relevant to desensitization of an individual to an allergen against which the individual mounts an allergic response, as recited in amended claim 1.

In response to Applicant's arguments, the enablement issue here is not simply intranodal injection of allergen to desensitize an individual, the tissues here are: the lack of guidance as to

the structure, much less function of any undisclosed "purified substance", "recombinant protein", "synthesized peptide", and *any* undisclosed "components" from bee venom, wasp venom, fire ant venom, pollen, mold, anesthetics, serum, drugs, animals, animal dander, cockroaches, dust mites, food allergen, poison ivy, poison oak, poison sumac, viruses, bacteria, protozoa, and latex because without amino acid sequence or SEQ ID NO has no structure. In the absence of guidance as to the structure and lack of sufficient in vivo working example, it is unpredictable that which undisclosed "substance", "recombinant protein", "synthesized peptide" and "components" of any allergen mentioned above are critical for the claimed method of desensitization. Further, there is insufficient guidance as to the structure and function of any adjuvant such as any surface active agent, surface active microparticle, bacterial product, cytokine, hormone, cellulose derivative, protein, and nucleic acid because of the lack of amino acid sequence or nucleotide sequence has no structure. Not only the lack of guidance as to structure of said adjuvant mentioned above for the claimed method, not all protein, nucleotide, cytokine, hormone and cellulose derivative would be useful as an adjuvant. Given the indefinite number of undisclosed protein, nucleotide, cytokine, hormone and cellulose derivative, it would take undue amount of experimentation to practice the claimed method. Although claim 1 has been amended to recite a method of desensitizing an individual to an allergen comprising delivering an allergen directly into a lymph node of said individual rather than modulating an immune response, amended claim 1 still fails to recite the step of how to deliver any allergen to any lymph node because intranodal injection requires the step of monitoring the location of the injection needle within the lymph node, which is critical for the claimed method. Further, the specification discloses only one allergen phospholipase A2 from bee venom for the claimed method. The specification merely mentioned the other allergen, much less about the specific "component" of any allergen.

5. Claims 1-10, 14, 19-26 and 45-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of desensitizing an individual to *any* allergen comprising the step of delivering any allergen against which the individual mounts an allergic response directly to any lymph node of said individual whereby the individual is desensitized to the allergen, (2) the said method wherein the lymph

node is an axillary lymph node or inguinal lymph node, (3) the said method wherein the allergen is allergen is deliver to an antigen presenting cell or an immune cell within the lymph node, (4) the said method further comprises the steps of using an ultrasound device to monitor location of an injection needle, (5) the said method further comprises the steps of visualizing the lymph node using a radiological method, (6) the said method wherein the allergen is *any* extract, or *any* "purified substance", *any* recombinant protein, *any* synthesized peptide, (7) the said method wherein the allergen is accompanied by an adjuvant such as *any* surface active agent, *any* surface active microparticle, *any* bacterial product, *any* cytokine, *any* hormone, any cellulose derivative, any protein, and any nucleic acid, (8) the said method wherein the step of delivering is carried out at least twice, (9) the said method wherein 1 to 5 doses of from about 0.01 μg to about 10 μg, or from about 0.1 μg to about 50 μg of the allergen is administered, (10) the said method wherein the allergen is deliver in fewer than about 10 doses, or from 1 to about 5 doses and (11) the said method wherein the allergen is delivered into the lymph node with a syringe or a dual-chambered syringe for desensitize an individual to *any* allergic response.

The specification discloses only a method of desensitizing an individual to an allergen comprising the step of delivering allergen wherein the allergen is phospholipase A2 which is an allergic component of bee venom against which the individual mounts an allergic response, directly to the lymph node such as the axillary lymph node or inguinal lymph node of said individual whereby the individual is desensitized to said allergen. The specification further discloses that an ultrasound device is used to monitor the location of the injection needle, and/or visualizing the lymph node using a radiological method. The specification discloses bee sting challenge only produces a minimum local reaction in a patient who has been desensitized.

With the exception of the specific allergen mentioned above, there is inadequate written description about the structure associated with function of *any* allergen such as "purified substance", *any* "recombinant protein" and *any* "synthesized peptide", *any* "components" from bee venom, wasp venom, fire ant venom, pollen, mold, anesthetics, serum, drugs, animals, animal dander, cockroaches, dust mites, food allergen, poison ivy, poison oak, poison sumac, viruses, bacteria, protozoa, and latex because of the lack of amino acid sequence or SEQ ID NO has no structure. Likewise, there is inadequate written description about the structure of any adjuvant such as *any* surface active agent, surface active microparticle, bacterial product, cytokine, hormone, cellulose derivative, or protein without the amino acid sequence and nucleic acid without the nucleotide sequence.

The specification discloses only one allergen that is phospholipase A2 from bee venom for the claimed method. Given that there is a lack of an additional species of allergen for the claimed method of desensitizing an individual, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of allergens to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 1/9/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the novel aspect of the invention is the intranodal injection of an allergen to desensitize an individual to the allergen. (2) Claims 1, 19, 21, 23 and 24 have been amended. (3) The specification explicitly discloses that an allergen can be any substance or portion thereof that elicits an allergic response...an allergens can be a mixture of substances or a crude or purified extract of a generally allergenic composition that recovered from a natural source or can be a synthetic or non-naturally occurring substance, such as recombinant protein, synthesized peptide, mimetic chemical (including peptide) that elicits an allergic response similar to a naturally occurring allergen.

In response to Applicant's arguments, there is inadequate written description about the structure associated with function of *any* allergen such as "purified substance", *any* "recombinant protein" and *any* "synthesized peptide", *any* "components" from bee venom, wasp venom, fire ant venom, pollen, mold, anesthetics, serum, drugs, animals, animal dander, cockroaches, dust mites, food allergen, poison ivy, poison oak, poison sumac, viruses, bacteria, protozoa, and latex because of the lack of amino acid sequence or SEQ ID NO has no structure. Likewise, there is inadequate written description about the structure of any adjuvant such as *any* surface active agent, surface active microparticle, bacterial product, cytokine, hormone, cellulose derivative, or protein without the amino acid sequence and nucleic acid without the nucleotide sequence.

The specification discloses only one allergen phospholipase A2 from bee venom, for the claimed method. The specification merely mentioned the other allergen, much less about the specific "component" of any allergen. Given the lack of an additional species of allergen for the claimed method of desensitizing an individual, one of skill in the art would reasonably conclude

that the disclosure fails to provide a representative number of species of allergens to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-5, 8-9, 14, 19-26 and 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong *et al* (J Immunological Methods 120: 151-7, June 1989; PTO 892) in view of Hellman *et al* (Handbook of Experimental Pharmacology 133(vaccines): 499-526, 1999; PTO 892), Coupey *et al* (Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (Immunol Rev 156: 199-209, April 1997; PTO 892).

Hong *et al* teach a method of modulating an immune response of an individual such as increasing the production of antigen specific IgG class monoclonal antibodies by delivering an antigen such as human serum albumin (Has) directly into a an inguinal lymph node by injection using a syringe (See entire document, Materials and methods, in particular). The reference inguinal lymph node immunization increases the magnitude of primary immune response against the specific antigen (See page 153, column 2, first paragraph, in particular). The reference antigen further comprises a delivery substance such as Freund's complete or incomplete adjuvant or aluminum (See page 153, column 1, last paragraph, page 155 Table II, in particular). The reference method wherein the reference HAS was injected at 0.1 μg, 0.5 μg, 1 μg, 5 μg, 10 μg or

50 μg per doses (See page 153, column 1, last paragraph, in particular). The reference method delivering is carried out at least twice (See booster shot, secondary immunization, abstract, in particular). Hong *et al* teach the inguinal lymph node immunizations induces strong primary immune response with limited amounts of antigen (See abstract, page 152, column 1, first paragraph, in particular).

The claimed invention as recited in claim 2 differs from the teachings of the reference only that the lymph node is axillary lymph node.

The claimed invention as recited in claim 4 differs from the teachings of the reference only that the allergen is deliver to an antigen presenting cell within the lymph node.

The claimed invention as recited in claim 5 differs from the teachings of the reference only that the allergen is delivered to an immune cell within the lymph node.

The claimed invention as recited in claims 8 and 46 differs from the teachings of the reference only that the individual possesses defective lymph nodes.

The claimed invention as recited in claim 9 differs from the teachings of the reference only that the allergen is an extract or a purified substance.

The claimed invention as recited in claim 14 differs from the teachings of the reference only that the allergen is selected from the group consisting of a recombinant protein and a synthesized peptide.

Hellman *et al* teach injection of the allergen such as pollen extract or recombinant protein or synthesized peptide can be effective for seasonal pollenosis by increasing allergen specific IgG, which is often correlated with reduced symptoms scores in the patient (See page 507, second paragraph, page 509, page 510, in particular). The increase in allergen specific IgG is the results of a shift in cytokine profile, with decreasing IL4 and IL-5 and increasing or unaffected levels of IFN-γ and IL-10 (See page 507, second paragraph, in particular). Hellman *et al* teach that allergen specific IgG due to an increase in IFNγ that redirect the immune response can significantly improve the clinical outcome for patient with chronic allergy and this beneficial effect can be maintained for a long time after the discontinuation of the therapy (See page 509, first paragraph, in particular).

Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) using a glass syringe; intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Coupey *et al* teach

that the reference method is useful in obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular).

Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes to present transported antigens to immune cells such as T and B cells within the lymph node in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antigen as taught by Hong *et al* for the allergen as taught by Hellman *et al* for a method of a method of desensitizing an individual to any allergen by delivering the allergen directly into the antigen presenting cell or immune cells within the lymph node as taught by Hong *et al*, Coupey *et al* and Zinkernagel *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Hong *et al* teach the inguinal lymph node immunizations induces strong primary immune response with limited amounts of antigen (See abstract, page 152, column 1, first paragraph, in particular). Hellman *et al* teach that injection of the allergen such as pollen extract can be effective for seasonal pollenosis by increasing allergen specific IgG, which is often correlated with reduced symptoms scores in the patient (See page 507, second paragraph, in particular). Coupey *et al* teach that intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular); the reference method is useful for obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular). Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes in order to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular). Claim 8 is included in this rejection because it is obvious that APC fails to migrate to the via the afferent lymph node in individual with defective lymph node since Zinkernagel *et al* teach antigens outside of the lymphoid tissues (lymph node) are immunologically ignored (See page 202, column 2, in

particular). Claim 21 is included in this rejection because the reference adjuvant alum is marketed in the form of aluminum hydroxide or phosphate. Claim 46 is included in this rejection because it is within the purview of one skilled in the art at the time the invention was made to use any syringe for injection as taught by Hellman *et al* and Coupey *et al.*

Applicants' arguments filed 1/9/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) ordinary artisan would not have been motivated to make the asserted combination because the primary is directed to generation of antibodies and contains no teachings of desensitization or allergic response. (2) Neither Coupey nor Zinkernagel address desensitization, (3) although Hellman teaches desensitization methods, Hellman does not teach any alternative to subcutaneous injection except for oral administration. (4) The Office action apparently equates increased IgG response with effective desensitization however, the ordinary artisan would have known that increasing IgG levels does not always correlate with successful desensitization as discloses by the enclosed references. (5) The ordinary artisan would not have reasonably expected, merely because intranodal injection of antigens increases IgG levels, that intranodal injection of an allergen could be used successfully to desensitize a patient against the allergen as recited in claims 1-5, 8-9, 14, 19-26, 45 and 46.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Hellman teaches desensitization methods. Hong *et al* teach the method of intranodal injection which were known at the time of filing. The specification discloses on page 14, line 12 that any methods can be used, such as "the technique used for injection is within the skill in the art". Further, Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Coupey *et al* further teach that the advantage of intranodal injection is useful in obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular) since it is well known at the time the invention was filed that large amount of allergen would trigger anaphylaxis, a dire consequence of immunotherapy.

In response to Applicant's arguments that the ordinary artisan would have known that increasing IgG levels does not always correlate with successful desensitization as discloses by the enclosed references, none of the enclosed references use intranodal injection of allergen.

In response to Applicant's arguments that the ordinary artisan would not have reasonably expected, merely because intranodal injection of antigens increases IgG levels could be used successfully to desensitized a patient against the allergen, the ordinary artisan would have known that the method of desensitizing an individual to any allergen involves a decreasing IL4 and IL-5 where the decrease in IL-4 is associated with a decrease in allergen specific IgE and a concomitant increase in interferon gamma which resulted in a shift in cytokine profile as taught by Hellman et al (See page 507, second paragraph, in particular). The ordinary artisan would have known that the injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections as taught by Coupey *et al* (See page 567, column 1, paragraph 2, in particular).

9. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hong *et al* (J Immunological Methods 120: 151-7, June 1989; PTO 892) in view of Hellman *et al* (Handbook of Experimental Pharmacology 133(vaccines): 499-526, 1999; PTO 892), Coupey *et al* (Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (Immunol Rev 156: 199-209, April 1997; PTO 892) as applied to claims 1-5, 8-9, 14, 19-26 and 45-46 mentioned above, and further in view of Banks *et al* (Chemistry and Pharmcology of Honey-bee venom In: Piek T, ed. Venoms of the Hyemoptera. London: Academic Press; 1986, pages 329-416).

The combined teachings of Hong *et al,* Hellman *et al,* Coupey *et al,* and Zinkernagel *et al* have been discussed supra.

The claimed invention as recited in claim 10 differs from the teachings of the references only that the allergen is the allergenic components of bee venom.

Banks *et al* teach a method of modulating an immune response (desensitization) comprising administering a small but increasing amounts of allergenic components such as phospholipase A2 (the chief allergen in bee venom), hyaluronidase, melittin and protease inhibitor (See Table II, in particular) of bee venom to build up the IgG levels in the serum of a

subject to inhibit an immune reaction (allergic reaction) against bee sting (See page 342, pages 331 and 403, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antigen as taught by Hong *et al* or the pollen allergen as taught by Hellman *et al* for the allergenic components of bee venom for a method of desensitizing an individual to bee venom as taught by Bank by delivering the allergen directly into a lymph node of any individual as taught by Hong *et al*, Coupey et al and Zinkernagel *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Banks *et al* teach administering a small but increasing amounts of allergenic components such as phospholipase A2 (the chief allergen in bee venom), hyaluronidase, melittin and protease inhibitor (See Table II, in particular) of bee venom can build up the IgG levels in the serum of a subject to inhibit an allergic response against bee sting (See page 342, pages 331 and 403, in particular). Coupey *et al* teach that the advantage of intranodal injection is useful in obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular).

Applicants' arguments filed 1/9/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) ordinary artisan would not have been motivated to make the asserted combination because the primary is directed to generation of antibodies and contains no teachings of desensitization or allergic response. (2) Neither Coupey nor Zinkernagel address desensitization, (3) although Hellman teaches desensitization methods, Hellman does not teach any alternative to subcutaneous injection except for oral administration. (4) The Office action apparently equates increased IgG response with effective desensitization however, the ordinary artisan would have known that increasing IgG levels does not always correlate with successful desensitization as discloses by the enclosed references. (5) The ordinary artisan would not have reasonably expected, merely because intranodal injection of antigens increases IgG levels, that intranodal injection of an allergen could be used successfully to desensitize a patient against the allergen as recited in claims 1-5, 8-9, 14, 19-26, 45 and 46. (6) The addition of Banks does not remedy the deficiencies of the combination and supplies neither a motivation to combine.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Hellman et al and Bank et al teach desensitization methods. Hong *et al* teach the method of intranodal injection which were known at the time of filing. The specification discloses on page 14, line 12 that any methods can be used, such as "the technique used for injection is within the skill in the art". Further, Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Coupey *et al* further teach that the advantage of intranodal injection is useful in obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular).

In response to Applicant's arguments that the ordinary artisan would have known that increasing IgG levels does not always correlate with successful desensitization as discloses by the enclosed references, none of the enclosed references use intranodal injection of allergen.

In response to Applicant's arguments that the ordinary artisan would not have reasonably expected, merely because intranodal injection of antigens increases IgG levels could be used successfully to desensitized a patient against the allergen, the ordinary artisan would have known that the method of desensitizing an individual to any allergen involves a decreasing IL4 and IL-5 where the decrease in IL-4 is associated with a decrease in allergen specific IgE and a concomitant increase in interferon gamma which resulted in a shift in cytokine profile as taught by Hellman et al (See page 507, second paragraph, in particular). The ordinary artisan would have known that the injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections as taught by Coupey *et al* (See page 567, column 1, paragraph 2, in particular).

In response to applicant's argument that there is no motivation to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching,

suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) And *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Hellman *et al* teach a method of desensitized an individual to allergen such as pollen by injection of pollen extract or recombinant protein or synthesized peptide to an individual, the reference method can be effective for seasonal pollenosis by increasing allergen specific IgG, which is often correlated with reduced symptoms scores in the patient (See page 507, second paragraph, page 509, page 510, in particular). Banks *et al* teach a method of desensitization comprising administering a small but increasing amounts of allergenic components such as phospholipase A2 (the chief allergen in bee venom), hyaluronidase, melittin and protease inhibitor (See Table II, in particular) of bee venom to build up the IgG levels in the serum of a subject to inhibit an immune reaction (allergic reaction) against bee sting (See page 342, pages 331 and 403, in particular).

Hong *et al* teach the method of intranodal injection which were known at the time of filing to increase the production of antigen specific IgG class monoclonal antibodies (See entire document, Materials and methods, in particular). The advantage of inguinal lymph node immunization increases the magnitude of primary immune response against the specific antigen (See page 153, column 2, first paragraph, in particular). Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Coupey *et al* teach the reference method is useful in obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular). Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular). The success in generating antigen specific antibody rapidly with low amounts of antigen as taught by Coupey and the increases in the magnitude of primary immune response against the specific antigen as taught by the Hong et al in the face of having to inject large amount of allergen that could lead to anaphylaxis in a subject as taught by Bank et al would have led one of ordinary skill in the art at

the time the invention was made to combine the references to solve a well known problem in the art. Further, Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular). The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) and see MPEP 2144.

10. Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong *et al* (J Immunological Methods 120: 151-7, June 1989; PTO 892) in view of Hellman *et al* (Handbook of Experimental Pharmacology 133(vaccines): 499-526, 1999; PTO 892), Coupey *et al* (Cytokine 5(6): 564-9, Nov 1993; PTO 892) and Zinkernagel *et al* (Immunol Rev 156: 199-209, April 1997; PTO 892) as applied to claims 1-5, 8-9, 14, 19-20, 22-26 and 45-46 mentioned above, and further in view of WO 99/02183 (Jan 1999; PTO 1449).

The combined teachings of Hong *et al,* Hellman *et al,* Coupey *et al,* and Zinkernagel *et al* have been discussed supra.

The claimed invention as recited in claim 6 differs from the teachings of the references only that the method step further comprising the use of an ultrasound device to monitor location of an injectable needle.

The claimed invention as recited in claim 7 differs from the teachings of the references only that the method further comprising the step of visualizing the lymph node using a radiological method.

The WO 99/02183 publication teaches a method of delivering any antigen to the inguinal lymph node by inserting a catheter or needle under ultrasonographic control to monitor the location of the needle (See page 58, lines 14-27, in particular). The WO 99/02183 publication further teaches radiography may be used to image a patient's lymphatic flow to determine where the relatively high lymphatic drainage occurs in order to decide upon an insertion position that maximizes delivery into the lymphatic system (See page 60, lines 28-33, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include the use of ultrasound device or radiographic method as taught by the WO 99/02183 publication for a method of modulating an allergic response of an individual comprising the step of delivering the allergen directly into a lymph node as taught by Hong *et al,* Hellman *et al,* Coupey *et al,* and Zinkernagel *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 99/02183 publication teaches the use of radiography can image a patient's lymphatic flow in order to decide upon an insertion position for maximizes delivery into the lymphatic system (See page 60, lines 28-33, in particular) and the ultrasonographic device can monitor the location of the needle (See page 58, lines 14-27, in particular).

Applicants' arguments filed 1/9/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) ordinary artisan would not have been motivated to make the asserted combination because the primary is directed to generation of antibodies and contains no teachings of desensitization or allergic response. (2) Neither Coupey nor Zinkernagel address desensitization, (3) although Hellman teaches desensitization methods, Hellman does not teach any alternative to subcutaneous injection except for oral administration. (4) The Office action apparently equates increased IgG response with effective desensitization however, the ordinary artisan would have known that increasing IgG levels does not always correlate with successful desensitization as discloses by the enclosed references. (5) The ordinary artisan would not have reasonably expected, merely because intranodal injection of antigens increases IgG levels, that intranodal injection of an allergen could be used successfully to desensitize a patient against the allergen as recited in claims 1-5, 8-9, 14, 19-26, 45 and 46. (6) The Office has used Applicant's teachings to select the elements of intranodal injection and an allergen from the cited references and to combine them as the present specification teaches. Hindsight use of Applicant's specification, however, is not permitted.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Hellman et al and Bank et al

teach desensitization methods. Hong *et al* teach the method of intranodal injection which were known at the time of filing. The specification discloses on page 14, line 12 that any methods can be used, such as "the technique used for injection is within the skill in the art". Further, Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Coupey *et al* further teach that the advantage of intranodal injection is useful in obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular).

In response to Applicant's arguments that the ordinary artisan would have known that increasing IgG levels does not always correlate with successful desensitization as discloses by the enclosed references, none of the enclosed references use intranodal injection of allergen.

In response to Applicant's arguments that the ordinary artisan would not have reasonably expected, merely because intranodal injection of antigens increases IgG levels could be used successfully to desensitized a patient against the allergen, the ordinary artisan would have known that the method of desensitizing an individual to any allergen involves a decreasing IL4 and IL-5 where the decrease in IL-4 is associated with a decrease in allergen specific IgE and a concomitant increase in interferon gamma which resulted in a shift in cytokine profile as taught by Hellman et al (See page 507, second paragraph, in particular). The ordinary artisan would have known that the injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections as taught by Coupey *et al* (See page 567, column 1, paragraph 2, in particular).

In response to applicant's argument that there is no motivation to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) And *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Hellman *et al* teach a method of desensitized an individual to allergen such as

pollen by injection of pollen extract or recombinant protein or synthesized peptide to an individual, the reference method can be effective for seasonal pollenosis by increasing allergen specific IgG, which is often correlated with reduced symptoms scores in the patient (See page 507, second paragraph, page 509, page 510, in particular). Banks *et al* teach a method of desensitization comprising administering a small but increasing amounts of allergenic components such as phospholipase A2 (the chief allergen in bee venom), hyaluronidase, melittin and protease inhibitor (See Table II, in particular) of bee venom to build up the IgG levels in the serum of a subject to inhibit an immune reaction (allergic reaction) against bee sting (See page 342, pages 331 and 403, in particular).

Hong *et al* teach the method of intranodal injection which were known at the time of filing to increase the production of antigen specific IgG class monoclonal antibodies (See entire document, Materials and methods, in particular). The advantage of inguinal lymph node immunization increases the magnitude of primary immune response against the specific antigen (See page 153, column 2, first paragraph, in particular). Coupey *et al* teach injection of popliteal lymph node (axillary lymph node) using a glass syringe and intralymph node immunization enables the antigen to trigger the immune system directly, preventing the tissue retention, catabolism and dilution observed with subcutaneous or intravenous injections (See page 567, column 1, paragraph 2, in particular). Coupey *et al* teach the reference method is useful in obtaining high titer antigen specific antibodies rapidly with low amounts of antigen (See page 567, column 1, paragraph 2, in particular). Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular). The success in generating antigen specific antibody rapidly with low amounts of antigen as taught by Coupey and the increases in the magnitude of primary immune response against the specific antigen as taught by the Hong et al in the face of having to inject large amount of allergen that could lead to anaphylaxis in a subject as taught by Bank et al would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. Further, Zinkernagel *et al* teach that antigen presenting cell (APC) with antigens must migrate via the afferent lymph to local lymph nodes (afferent lymph nodes) to present transported antigens to immune cells such as T and B cells in order for T cells to be sensitized to the specific

antigen since antigens outside of the lymphoid tissues are immunologically ignored (See page 202, column 2, in particular). The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) and see MPEP 2144.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any

inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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Technology Center 1600
March 24, 2003

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